Reaction of 2-(Polyfluoroacyl)cycloalkanones with Hydroxylamine

by **Dmitri V. Sevenard***[a]), **Oleg G. Khomutov**[b]), **Kazimir I. Pashkevich**[b]), **Enno Lork**[a]), and **Gerd-Volker Röschenthaler**[a])

[a]) Institute of Inorganic and Physical Chemistry, University of Bremen, Leobener Strasse, D-28334 Bremen (e-mail: sevenard@chemie.uni-bremen.de; fax: +49-421-218-4267; tel.: +49-421-218-3435)

[b]) Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences, 20 ul. S. Kovalevskoi, 620219 Ekaterinburg, Russia

The 2-acylcycloalkanones **1a**–**g** and **3a**–**c**, possessing a polyfluoroalkyl group, react with hydroxylamine regio- and stereoselectively to yield 4,5-dihydroisoxazol-5-ols **2a**–**g** and **4a**–**c**, respectively, *i.e.*, products of N-addition to the oxo group at the cycloalkane ring (*Schemes 1* and *2*). The products **2** and **4** can be dehydrated under drastic conditions only (*Schemes 3* and *4*). The structure of one of the 4,5-dihydroisoxazol-5-ols was confirmed by X-ray crystal-structure analysis.

Introduction. – The interaction of 1,3-dicarbonyl compounds with hydroxylamine is considered to be one of the basic synthetic routes to isoxazole derivatives [1], which possess significant chemical potential [1][2], as well as various biological activities [3].

For a nonsymmetrical 1,3-dicarbonyl substrate in this reaction, the formation of regioisomers is possible. Thus, in the case of 2-acetylcyclohexanone, a mixture of isomeric 3-methyl- and 5-methylisoxazoles was obtained [4][5]. The introduction of a polyfluorinated substituent in the 1,3-dicarbonyl compound results in a significant change of the electron-density distribution and consequently in a change of relative reactivity of the two carbonyl groups. The reaction of linear polyfluoroalkyl 1,3-diketones with hydroxylamine occurs unambigously affording 4,5-dihydro-5-(polyfluoroalkyl)isoxazol-5-ols exclusively – an intermediate step in the 5-(polyfluoroalkyl)isoxazole formation. The dihydroisoxazolols represent stable compounds that may be dehydrated to the corresponding isoxazoles under drastic conditions only [6–8]. Moreover, 2-(trifluoroacetyl)- and 2-(polychloroacetyl)-substituted cyclohexanones [5], triterpen-3-ones [9], and homoadamantanone [10] are known to give 4,5-dihydro-5-R^{Hal}-isoxazol-5-ols, 5-(trifluoromethyl)isoxazoles, or 3-(trifluoromethyl)isoxazoles in the reaction with hydroxylamine, depending on the size of the carbocyclic ring in the 1,3-diketone molecule and on the reaction conditions.

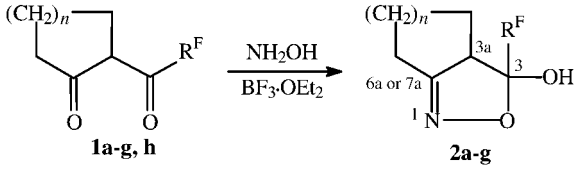
Among the 2-acyl-substituted cycloalkanones, the cyclopentanone derivatives represent a special case, forming an alternative product – 4,5-dihydro-3-R-isoxazol-5-ols – in the reaction with hydroxylamine, independent of the presence of F-atoms in the RC=O moiety [11]. In the case of 2-(trifluoroacetyl)cyclopentanone, the dioxime [11], which cyclizes in acidic medium only, was also isolated.

The present work aimed at the investigation of the chemical behavior of a variety of 2-(polyfluoroacyl)cycloalkanones in the reaction with hydroxylamine, the former differing in ring size, (polyfluoroalkyl)-radical length, and the presence of substituents at the cycloalkane ring. The expected products of such reactions can possess a set of

practically useful properties. The 5-(polyfluoroalkyl)isoxazoles obtained from linear nonsymmetrical 1,3-diketones are known to be used as surfactants and high temperature heat carriers [6].

Results and Discussion. –The 2-(polyfluoroacyl)cycloalkanones **1a–g** were found to react regiospecifically with hydroxylamine in the presence of a catalytic amount of $BF_3 \cdot OEt_2$ (*Scheme 1*). Independent of ring size and polyfluoroalkyl-substituent length, 4,5-dihydro-5-R^F-isoxazol-5-ols **2a–g** were formed exclusively as products of amino-group addition to the carbonyl group of the cycloalkane ring followed by a cyclization.

Scheme 1



1a-g, h **2a-g**

1, 2	*n*	R^F
a	1	CF_2CF_2H
b	1	C_4F_9
c	2	CF_3
d	2	CF_2CF_2H
e	2	C_3F_7
f	2	$(CF_2)_4H$
g	2	C_6F_{13}
h	1	CF_3

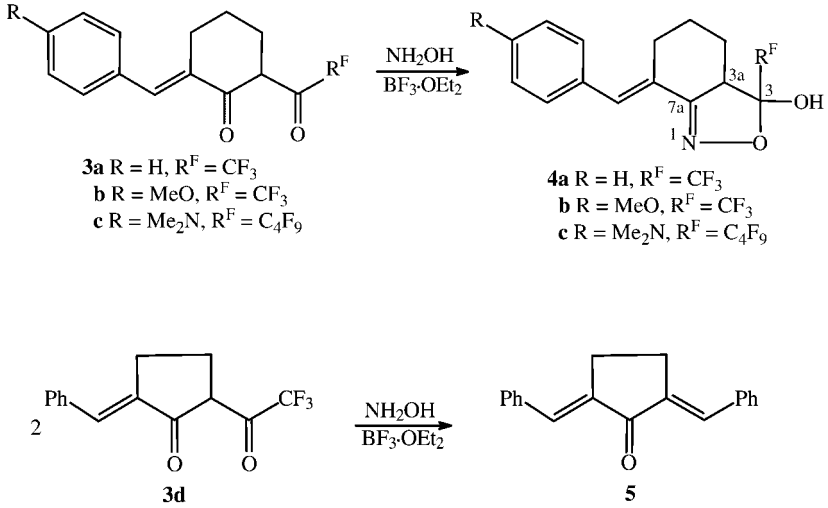
The only exception among the 1,3-diketones **1** was 2-(trifluoroacetyl)cyclopentanone **1h**. In this case, the reaction afforded a complex mixture of several compounds (according to ^{19}F-NMR data). The MS of this mixture shows a set of signals that could be ascribed to a possible 1:1 adduct of **1h** and hydroxylamine (*m/z* 195 (60, M^+), 178 (30, $[M - OH]^+$), 108 (100, $[M - H_2O - CF_3]^+$). Unfortunately, this data did not allow us to unequivocally assign the structure of this compound. The unusual behavior of 1,3-diketone **1h** in the reaction under consideration has already been reported [11]. However, we failed to reproduce the results given in [11]. Reaction of **1h** with hydroxylamine, in the presence of both pyridine and 20% hydrochloric acid, resulted in a complex mixtures of compounds.

An attempt to synthesize a 3-(trifluoroacetyl)isoxazole derivative (as a product of an amino-group attack on a trifluoroacetyl moiety), isomeric to the compounds **2**, by treating 1,3-diketone **1c** with hydroxylamine in the presence of NaOH according the procedure in [10], failed, too. An unseparable mixture of several products was obtained.

Previously, we presented the synthesis of (polyfluoroalkyl)-containing (*E*)-alk-4-ene-1,3-diones [12]. These compounds, having several unequal electrophilic centers, proved to be valuable building blocks in the synthesis of various heterocycles [13][14]. Now we have found that (*E*)-alk-4-ene-1,3-diones **3a–c** react with hydroxylamine in the presence of $BF_3 \cdot OEt_2$ at the 1,3-dione moiety exclusively, furnishing the corresponding 4,5-dihydro-5-R^F-isoxazol-5-ol derivatives **4a–c** (*Scheme 2*). Notewor-

thy is that, in this case, the yields of products depended on the length of the (polyfluoroalkyl)-substituent in the substrate molecule. For CF_3-substituted compounds, the yields were 58% (**4a**) and 71% (**4b**), whereas, for **4c** with $R^F = C_4F_9$, the yield was 15% only.

Scheme 2



The (*E*)-4-benzylidene-1,3-dione **3d** reacted otherwise with hydroxylamine (*Scheme 2*). In this case, the reaction proceeded unselectively, and we managed to isolate 2,5-dibenzylidenecyclopentanone (**5**) in 32% yield from a mixture of several products. Compound **5** is formed probably by fragmentations (*retro*-aldol degradation, ketone cleavage of 1,3-diketone) and recondensation [15].

The structure of compound **2a** in the crystal state was confirmed by X-ray-diffraction analysis. Selected bond lengths and angles are listed in *Tables 1* and *2*. An ORTEP-style view is shown in the *Figure*. The dihydroisoxazole moiety has an envelope conformation with the C(6) atom (arbitrary numbering) deviating from the plane formed by the other ring atoms by 40.0 pm. The OH group at C(6) is *cis*-oriented with respect to the CH_2(5) substituent and occupies a pseudo-axial position (torsion angle C(2a)–C(5a)–C(6)–O(2) –98.9°). The 1,1,2,2-tetrafluoroethyl substituent has a pseudo-equatorial orientation (torsion angle C(2a)–C(5a)–C(6)–C(7) 137.1°). Also, the cyclopentane ring has an envelope conformation, the C(5) atom deviating from the plane formed by the other ring atoms by 58.9 pm. The atoms C(5) and C(6) deviate from the plane N(1)–C(2a)–C(3)–C(5a) by 80.0 and 56.1 pm, respectively.

The IR spectra of **2a**,**c**–**g** (*Table 3*) in the solid state show an absorption band at 1625 cm^{-1}, which is attributed to the C=N vibration, and a broad band near 3000–3650 cm^{-1} due to the OH-group adsorption. As all the IR spectra exhibit the same features, it is suggested that all compounds **2** have a 4,5-dihydroisoxazole structure in the solid state, as extrapolated from the X-ray crystal structure of **2a** (see above).

In ^{1}H-, ^{13}C-, and ^{19}F-NMR spectra (*Tables 4–7*) of the reaction products of 2-(polyfluoroacyl)cycloalkanones with hydroxylamine, only one set of signals was

Table 1. *Selected Bond Lengths of* **2a**. For numbering, see *Figure.*

	d/pm		*d*/pm
O(1)–N(1)	144.28(17)	C(3)–C(4)	154.4(2)
O(1)–C(6)	145.61(17)	C(4)–C(5)	154.5(2)
O(2)–C(6)	137.71(17)	C(5a)–C(6)	152.6(2)
N(1)–C(2a)	126.4(2)	C(5a)–C(5)	153.0(2)
C(2a)–C(5a)	149.4(2)	C(6)–C(7)	153.5(2)
C(2a)–C(3)	150.1(2)		

Table 2. *Selected Bond Angles of* **2a**. For numbering, see *Figure.*

	ω/degrees		ω/degrees
N(1)–O(1)–C(6)	107.98(10)	C(6)–C(5a)–C(5)	124.22(12)
C(2a)–N(1)–O(1)	107.43(11)	C(5a)–C(5)–C(4)	101.92(12)
N(1)–C(2a)–C(5a)	115.10(13)	O(2)–C(6)–O(1)	110.98(11)
N(1)–C(2a)–C(3)	131.62(14)	O(2)–C(6)–C(5a)	117.40(12)
C(5a)–C(2a)–C(3)	112.11(13)	O(1)–C(6)–C(5a)	102.77(11)
C(2a)–C(3)–C(4)	101.95(12)	O(2)–C(6)–C(7)	104.30(11)
C(3)–C(4)–C(5)	106.52(12)	O(1)–C(6)–C(7)	105.11(11)
C(2a)–C(5a)–C(6)	99.92(11)	C(5a)–C(6)–C(7)	115.74(11)
C(2a)–C(5a)–C(5)	102.37(12)		

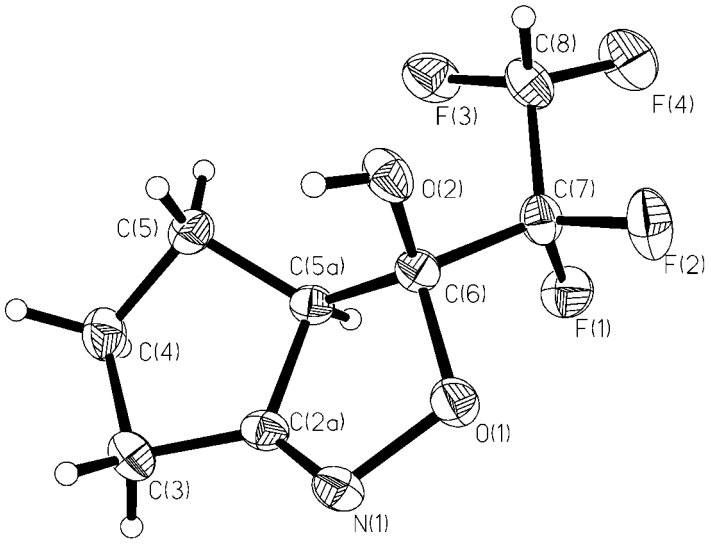


Figure. *Molecular structure of compound* ***2a*** (ORTEP-style view). Arbitrary numbering.

Table 3. *Selected IR Data* (vaseline oil) *of Compounds* **2a**, **c**–**g**. $\tilde{\nu}$ in cm^{-1}.

	2a	**2c**	**2d**	**2e**	**2f**	**2g**
$\tilde{\nu}$ (C=N)	1625	1625	1625	1625	1625	1625
$\tilde{\nu}$ (O–H) (br.)	3000–3650	3000–3350	3000–3400	3000–3400	3000–3350	3000–3350

revealed. This means that the condensation product (dielectrophile + NH_2OH (1:1) with elimination of one H_2O molecule) exists in (D_6)DMSO solution as only one of possible tautomeric (or isomeric) forms: 4,5-dihydroisoxazol-5-ol, 2,5-dihydroisoxazol-5-ol, 2,3-dihydroisoxazol-3-ol, β-ketone oxime, or β-hydroxylamino-enone [5][10][11][16].

The ^{1}H-NMR spectra (*Tables 4* and *5*) of **2a**,**b**,**d**–**g** and **4a**–**c** show signals corresponding to the methine proton H–C(3a) (δ(H) 3.1–4.0) and the OH group (δ(H) *ca.* 8). In the ^{13}C-NMR spectra (*Table 6*), C(3) is observed at δ(C) *ca.* 104, the assignment being certain because of splitting with ^2J(C,F); the chemical-shift value lead to the assumption about a hemiacetal character of the corresponding C-atom. The signal of C(6a) of **2a**,**b** or of C(7a) of **2f**,**g** and **4a**–**c** is observed in the range δ(C) 160.0–173.3, indicating that this atom belongs to the oxime moiety. This finding, taken together with the ^{1}H-NMR data discussed above, allows us to exclude the alternative structural moieties ascribed to related compounds [11][16]. Thus, we conclude that our compounds exist as 4,5-dihydro-5-R^F-isoxazol-5-ols both in the solid state and in solution.

The presence of a single signal set in the NMR spectra of compounds **2a**–**g** and **4c** is strong evidence of a high degree of stereoselectivity of the reaction discussed. However, the ^{19}F-NMR spectra of **4a**,**b** (*Table 7*) show, besides the main CF_3 signal an additional CF_3 resonance at δ(F) −80.9 (only *one* set of ^{1}H- and ^{13}C-NMR signals), with an integral ratio 2:98 of this additional signal to the main signal of the major 4,5-dihydroisoxazol-5-ol. Nevertheless, it is scarcely possible to conclude whether this additional signal arises from an other stereo- or regioisomer.

Table 4. *^{1}H-NMR Data* ((D_6)DMSO) *of Compounds* **2a**,**b**,**d**–**g**[a]). δ(H) in ppm, *J* in Hz.

	$(CH_2)_{n+2}$	H–C(3a)	R^F (1 H)	OH
2a	1.52–1.84 (*m*, CH_2); 2.09–2.42 (*m*, 2 CH_2)	3.89 (*t*, ^3J(H,H) = 9.9)	6.49 (*tdd*, ^2J(H,F) = 51.8, ^3J(H,F_a) = 8.2, ^{3}J (H,F_b) = 4.5	8.14 (*s*)
b	1.60–1.91 (*m*, CH_2); 2.15–2.58 (*m*, 2 CH_2)	4.03 (*t*, ^3J(H,H) = 9.8)	–	8.46 (*s*)
d	1.23–2.48 (*m*, 4 CH_2)	3.13–3.30 (*m*)	6.53 (*tt*, ^2J(H,F) = 51.6, ^3J(H,F) = 6.5)	7.91 (*s*)[b])
e	1.09–2.53 (*m*, 4 CH_2)	3.1–3.6 (*m*)	–	8.3 (br. *s*)
f	1.35–2.53 (*m*, 4 CH_2)	3.07–3.40 (*m*)	6.94 (*tt*, ^2J(H,F) = 50.6, ^3J(H,F) = 5.9)	8.08 (*s*)
g	1.15–2.54 (*m*, 4 CH_2)	3.2–3.5 (*m*)	–	8.18 (*s*)

[a]) For the ^{1}H-NMR data of **2c**, see [5]. [b]) The signal disappeared after CD_3COOD addition.

Table 5. *^{1}H-NMR Data* ((D_6)DMSO) *of Compounds* **4a**–**c**. δ(H) in ppm, *J* in Hz.

	$(CH_2)_3$	H–C(3a)	CH=C(7)	Ar	OH
4a	1.39–1.60 (*m*, 1 H); 1.75–1.81 (*m*, 3 H); 2.21–2.35 (*m*, 1 H); 2.85 (*d*, *J*(H,H) = 15.2, 1 H)	3.48 (*dd*, ^3J(H,H) = 10.0, 7.1)	7.09 (*s*)	7.30–7.75 (*m*)	8.33 (*s*)
b	1.36–1.61 (*m*, 1 H); 1.75–1.95 (*m*, 3 H); 2.29 (*t*, *J*(H,H) = 14.2, 1 H); 2.86 (*d*, *J*(H,H) = 14.2, 1 H)	3.48 (*dd*, ^3J(H,H) = 10.3, 7.3)	7.06 (*s*)	3.78 (*s*, Me); 6.97, 6.36 (*AB*, *J*(H_A,H_B) = 8.6, C_6H_4)	8.31 (*s*)
c	1.36–1.63 (*m*, 1 H); 1.72–1.96 (*m*, 3 H); 2.27 (*t*, *J*(H,H) = 14.2, 1 H); 2.86 (*d*, *J*(H,H) ≈ 14, 1 H)	3.46 (*t*, ^3J(H,H) = 8.6)	6.97 (*s*)	2.92 (*s*, 2 Me); 6.70, 7.26 (*AB*, *J*(H_A,H_B) = 8.8, C_6H_4)	8.42 (*s*)

Table 6. *^{13}C-NMR Data* ((D$_6$)DMSO) *of Compounds* **2a**,**b**,**f**,**g** *and* **4a**–**c**[a]). δ(C) in ppm, J in Hz.

	$(CH_2)_m$	C(3a)	C(3)	R^F	C(6a) or C(7a)	ArCH=C
2a	21.8, 22.0, 29.4 (3*s*)	59.3 (*s*)	104.3 (*ddd*, ^2J(C,F$_A$) = 26.3, ^2J(C,F$_B$) = 22.6, ^3J(C,F$_M$) = 0.8)	110.1 (*dddd*, ^1J(C,F$_A$) = 249.8, ^1J(C,F$_B$) = 247.6, ^2J(C,F$_M$) = 33.2, ^2J(C,F$_N$) = 28.7); 114.62 (*tdd*, ^1J(C,F) = 255.6, ^2J(C,F$_A$) = 25.6, J(C,F$_B$) = 23.7)	173.3 (*s*)	–
b	20.8, 21.0, 28.4 (3*s*)	58.8 (*s*)	104.1 (*dd*, ^2J(C,F$_A$) = 26.7, ^2J(C,F$_B$) = 21.9)	107.0–126.3 (*ms*)	172.4 (*s*)	–
f	23.6, 24.9, 25.1, 25.4 (4*s*)	51.6 (*s*)	105.2 (*t*, ^2J(C,F) = 25.1)	108.9 (*tt*, ^1J(C,F) = 251.1, ^2J(C,F) = 30.3); 111.14 (*tm*, ^1J(C,F) = 263.7); 112.09 (*tm*, ^1J(C,F) = 266.6); 114.86 (*tt*, ^1J(C,F) = 261.3, ^2J(C,F) = 30.3)	160.8 (*s*)	–
g	23.6, 24.9, 25.1, 25.4 (4*s*)	51.6 (*s*)	105.4 (*t*, ^2J(C,F) = 25.8)	106.7–121.8 (*ms*)	160.9 (*s*)	–
4a	22.4, 22.7, 27.4 (3*s*)	50.4 (*s*)	103.0 (*q*, ^2J(C,F) = 32.1)	122.7 (*q*, ^1J(C,F) = 284.2)	159.9 (*s*)	127.8, 128.0, 128.4, 128.8, 129.6, 135.2 (6*s*)
b	22.4, 22.7, 27.4 (3*s*)	50.4 (*s*)	102.9 (*q*, ^2J(C,F) = 31.8)	122.7 (*q*, ^1J(C,F) = 284.9)	160.0 (*s*)	55.1 (*s*, Me); 113.9, 125.6, 127.7, 128.6, 131.2, 159.0 (6*s*, C_6H_4CH=C)
c	22.6, 22.9, 27.5 (3*s*)	50.9 (*s*)	105.6 (*dd*, ^2J(C,F$_A$) = 27.6, ^2J(C,F$_B$) = 24.9)	111.4–121.1 (*ms*)	159.9 (*s*)	39.7 (*s*, Me); 111.6, 122.9, 122.9, 129.3, 131.0, 149.8 (6*s*, C_6H_4CH=C)

[a]) For the ^{13}C-NMR data of **2c**, see [5].

According to the proposed structures, the CH_2 protons and F-atoms of the CF_2 groups are magnetically nonequivalent. Thus, the H–C(3a) signal of **4a**,**b** appears as a *dd* (*Table 5*). In the ^{19}F-NMR spectra of **2b**,**d**,**f**,**g** and **4c**, the signals of the CF_2 groups of the R^F substituent bonded to the stereogenic center appear as *AB* systems (*Table 7*). For **2a**, all the F-atoms are nonequivalent and form an *ABMNX* spin system with the polyfluoroalkyl proton (see *Tables 4* and *7*). Due to the nonequivalence of the F-atoms, the C(3) signal appears as a *dd* (^2J(C,F$_A$) and ^2J(C,F$_B$)) in the spectra of **2a**,**b** and **4c**. In the ^{13}C-NMR spectrum of **2a**, the signals of the C-atoms of the 1,1,2,2-tetrafluoroethyl group are split into a *tdd* and a *dddd* (see *Tables 6* and *7*).

The MS data (*Table 8*) of **2b**,**g** and **4a**–**c** confirm the proposed structures.

Compounds **2a**–**g** and **4a**–**c** proved to be rather stable under dehydration conditions. This finding coincides with the known stabilization of such hydroxy derivatives by a polyfluoroalkyl substituent geminal to the OH group [16–20]. After treatment of **2c** in CH_2Cl_2 with a catalytic amount of hydrochloric acid (under these

Table 7. *^{19}F-NMR Data* ((D$_6$)DMSO) *of Compounds* **2a**,**b**,**d**,**f**,**g** *and* **4a**–**c**. δ (F) in ppm, J in Hz.

2a	−129.08, −131.44, −138.15, −140.67 (*A*, *B*, *M*, and *N* of *ABMNX*, resp., $J(F_A,F_B)=264$, $J(F_M,F_N)=301$, $J(F_A,F_M)=12.1$, $J(F_A,F_N)=6.9$, $J(F_A,H_X)=8.2$, $J(F_B,F_M)=0$, $J(F_B,F_N)=10.3$, $J(F_B,F_X)=4.5$, $J(F_M,H_X)=J(F_N,H_X)=51.8$, 2 CF_2)
b	−127.6, −126.6 (*AB* of *m*, $J(F_A,F_B)=292.0$, CF_2); −123.0, −122.6 (*AB* of *m*, $J(F_A,F_B)=299.1$ CF_2); −124.2, −118.6 (*AB* of *m*, $J(F_A,F_B)=278.5$, CF_2); −81.61 (*t*, $^4J(F,F)=9.5$, CF_3)
d	−137.96 (*dt*, $^2J(F,H)=52.2$, $^3J(F,F)=7.8$, CF_2H); −131.1, −129.6 (*AB*, $J(F_A,F_B)=266.4$,$^3J(F,F)\approx 8$, CF_2)
f	−123.95, −121.55 (*AB* of *t*, $J(F_A,F_B)=282.8$, $^4J(F,F)=11.2$, CF_2); −123.5 (br. *s*, CF_2); −131.26 (*m*, CF_2); −139.61 (*d*, $^2J(F,H)=50.0$, CF_2H)
g	−127.3, −123.9, −123.2 (3 br. *s*, 3 CF_2); −121.67 (*m*, CF_2); −123.56, −121.10 (*AB* of *t*, $J(F_A,F_B)=269.0$, $^4J(F,F)\approx 10$, CF_2); −81.80 (*t*, $^4J(F,F)=9.5$, CF_3)
4a	−81.59 (*s*)[a])
b	−81.55 (*s*)[b])
c	−127.47, −126.55 (*AB* of *t*, $J(F_A,F_B)=289.7$, $^4J(F,F)=13.8$, CF_2); −122.03, −120.33 (*AB* of *t*, $J(F_A,F_B)=281.0$, $^4J(F,F)=12.1$, CF_2); −122.19 (*m*, CF_2); −81.59 (*t*, CF_3, $^4J(F,F)=9.5$, CF_3)

[a]) An additional *s* (δ(F) −80.89) was found, 2 : 98 integral ratio of this *s* and the *s* at δ(F) −81.59. [b]) An additional *s* (δ(F) −80.96) was found, 2 : 98 integral ratio of this *s* and the *s* at δ(F) −81.55.

Table 8. *Selected EI-MS Data of Compounds* **2b**,**g**, **4a**–**c**, **6a**,**b**, *and* **7a**–**c**

	m/*z* (%)
2b	345 (40, M^+), 327 (8, $[M-H_2O]^+$), 219 (3, $C_4F_9^+$), 169 (5, $C_3F_7^+$), 119 (5, $C_2F_5^+$), 98 (100, $C_5H_8NO^+$), 69 (38, CF_3^+), 18 (36, H_2O^+), and other fragments
g	459 (5, M^+), 169 (2, $C_3F_7^+$), 140, (40, $[M-C_6F_{13}]^+$), 122 (48, $[M-C_6F_{13}-H_2O]^+$), and other fragments
4a	296 (100, M^+), 279 (2, $[M-OH]^+$), 77 (10, $C_6H_5^+$), 18 (18, H_2O^+), and other fragments
b	326 (100, M^+), 309 (1, $[M-OH]^+$), and other fragments
c	490 (100, M^+), 472 (7, $[M-H_2O]^+$), 69 (7, CF_3^+), 18 (7, H_2O^+), and other fragments
6a	323 (30, M^+), 172 (10, $[M-C_3F_6H]^+$), 122 (100, $[M-C_4F_8H]^+$), and other fragments
b	441 (33, M^+), 172 (15, $[M-C_5F_{11}]^+$), 122 (100, $[M-C_6F_{13}]^+$), 69 (30, CF_3^+), and other fragments
7a	279 (58, M^+), 260 (6, $[M-F]^+$), 210 (100, $[M-CF_3]^+$), 77 (10, $C_6H_5^+$), and other fragments
b[a])	388 (100, $[M-H]^-$), 81 (8, SO_3H^-), and other fragments (negative) 505 (100), 372 (8, $[M-OH]^+$), and other fragments (positive)
c	309 (23, M^+), 240 (50, $[M-CF_3]^+$), 18 (100, H_2O), and other fragments

[a]) FAB.

conditions, the analogous 4,5-dihydro-5-(polyfluoroalkyl)-1*H*-pyrazol-5-ols were successfully dehydrated [21]), the starting compound was isolated quantitatively. Heating **4b** in AcOH also gave no result. The desired dehydration took place only under harsher conditions, namely on heating in conc. sulfuric acid. But even in this case, several hours were necessary for the reaction to be completed. Thus, 30 min heating of **2c** in conc. H_2SO_4 solution resulted in a 80% conversion, and after only 5 h heating, the reaction was complete [5]. The dehydration of the **2f**,**g** and **4a** under the above conditions afforded previously unknown isoxazole derivatives **6a**,**b** and **7a**, respectively (see *Scheme 3*, *Tables 8–10*).

Scheme 3

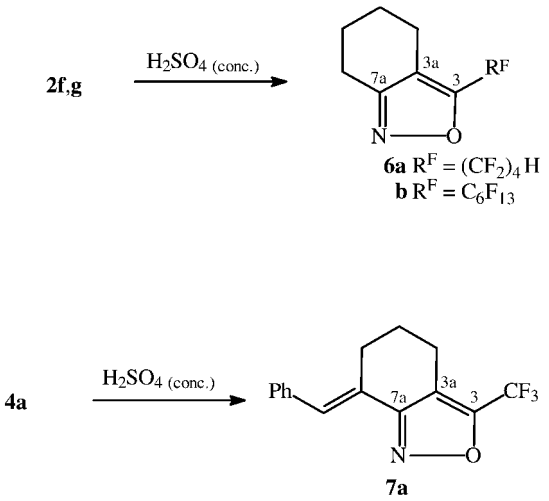


Table 9. *^{1}H- and ^{19}F-NMR Data* ($CDCl_3$) *of Compounds* **6a**, **6b**, *and* **7a**–**c**. δ(H) and δ(F) in ppm, J in Hz.

	δ(H)			δ(F)
	$(CH_2)_n$	Ar	CH=C(7)	
6a[a])	1.65–1.91 (*m*, 2 CH_2); 2.52–2.66 (*m*, CH_2); 2,74 (*t*, ^3J(H,H) = 6.1, CH_2)	–	–	– 139.08 (*d*, ^2J = 51.7, CF_2H); – 131.56, 126.31, – 114.66 (3*s*, 3 CF_2)
b	1.69–1.90 (*m*, 2 CH_2); 2.62–2.73 (*m*, CH_2); 2.81 (*t*, ^3J(H,H) = 6.2, CH_2)	–	–	– 127.51, – 123.40 (2*s*, 2 CF_2); – 124.16 (*m*, 2 CF_2); – 114.12 (*t*, ^4J(F,F) = 12.9, CF_2); – 82.18, CF_3)
7a	1.73–1.91 (*m*, CH_2); 2.64–2.88 (*m*, 2 CH_2)	7.28–7.45 (*m*)	7.65 (*s*)	– 64.35 (*s*)
b[b])	1.69–1.84 (*m*, CH_2); 2.70–2.82 (*m*, 2 CH_2)	3.79 (*s*, Me); 7.02, 7.43, and 7.86 (*A*, *B*, and *X* of *ABX*, $J(H_A,H_B)$ = 8.3, $^4J(H_A,H_X)$ = 1.5, $^4J(H_B,H_X)$ = C_6H_3)	7.46 (*s*)	– 63.44 (*s*)
c	1.75–1.88 (*m*, CH_2); 2.69–2.82 (*m*, 2 CH_2)	3.83 (*s*, Me); 6.88–6.96, 7.32–7.39 (2*m*, C_6H_4)	7.58 (*s*)	– 64.35 (*s*)

[a]) $(CF_2)_4H$: 6.05 (*tt*, ^2J(H,F) = 52.0, ^3J(H,F) = 5.3). [b]) In (D_6)DMSO.

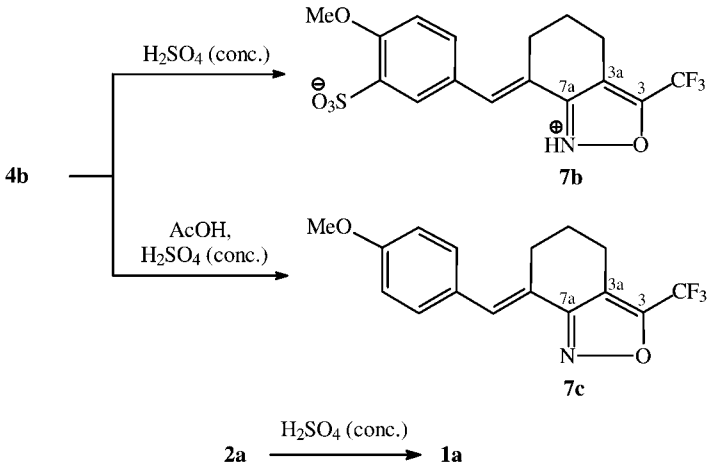
Upon heating of compound **4b** in conc. sulfuric acid, not only heteroaromatization, but also benzene-ring sulfuration (most likely in the *o*-position to the MeO group) occurred. The product, sulfonic acid **7b**, existing as a zwitterion and polyhydrate, was obtained in 31% yield (*Scheme 4*). 'Normal' dehydration of **4b** took place upon heating in AcOH/conc. H_2SO_4 solution for 3 h. In this case, isoxazole **7c** was obtained in 54% yield (*Scheme 4*, *Tables 8–10*).

Table 10. *^{13}C-NMR Data* ($CDCl_3$) *of Compounds* **6a**,**b** *and* **7a**–**c**. δ(C) in ppm, *J* in Hz.

Product	$(CH_2)_n$	R^F	C(3a)	C(3)	C(7a)	ArCH=C
6a	19.3, 21.7, 21.9, 22.0 (4*s*)	108.0 (*tt*, ^1J(C,F) = 254.3, ^2J(C,F) = 31.1); 110.5 (*tt*, ^2J(C,F) = ^1J(C,F) = 264.1, ^2J(C,F) = 31.1); 111.1 (*tt*, ^1J(C,F) = 265.5, ^2J(C,F) = 30.6); 112.4 (*tt*, ^1J(C,F) = 255.8, ^2J(C,F) = 33.1)	119.2 (*s*)	151.4 (*t*, $^2J(C,F)$ = 31.8)	162.0 (*s*)	–
b	19.0, 21.5, 21.6, 22.0 (4*s*)	102.1–120.6 (*ms*)	118.9 (*s*)	151.0 (*t*, ^2J(C,F) = 31.6)	161.6 (*s*)	–
7a	19.1, 22.7, 26.7 (3*s*)	118.7 (*q*, ^1J(C,F) = 270.3)	117.0 (*q*, ^3J(C,F) = 1.9)	152.1 (*q*, ^2J(C,F) = 41.3)	160.5 (*s*)	125.1, 127.9, 128.4, 129.0, 129.6, 135.7 (6*s*)
b[a])	18.2, 21.9, 26.0 (3*s*)	119.5 (*q*, ^1J(C,F) = 269.8)	118.1 (*q*, ^3J(C,F) = 1.7)	151.0 (*q*, ^3J(C,F) = 40.5)	160.5 (*s*)	55.5 (*s*, Me); 111.8, 123.0, 126.0, 132.1, 135.8, 129.6, 128.0, 156.2 (*s*, C_6H_3CH=C)
c	19.1, 22.6, 26.7 (3*s*)	118.7 (*q*, ^1J(C,F) = 270.0)	116.9 (*q*, ^3J(C,F) = 2.0)	151.8 (*q*, ^2J(C,F) = 41.3)	160.7 (*s*)	55.3 (*s*, Me); 113.8, 123.1, 128.3, 128.6, 131.1, 159.3 (6*s*, C_6H_4CH=C)

[a]) In (D_6)DMSO.

Scheme 4



The behavior of the cyclopentane-containing compound **2a** under dehydration conditions differed drastically from that of the corresponding 4,5-dihydroisoxazol-5-ols having a cyclohexane moiety. Upon heating **2a** in conc. sulfuric acid, no isoxazole formation was observed. Along with the starting material, 1,3-diketone **1a** was isolated

(*Scheme 4*). The opening of the heterocycle apparently results from the instability of a system of two condensed 5-membered rings with two exocyclic double bonds in one of them [22].

Thus, the interaction of 2-(polyfluoroacyl)cycloalkanones with hydroxylamine proceeds according to the hardness concept [23] (for the related reaction of ethyl 4,4,4-trifluoroacetoacetate, see [20]). The softer basic center (an amino group of the nucleophile) reacts with the softer acidic center (oxo group of the cycloalkane ring) and, correspondingly, the harder acidic center with the harder basic one. The dehydration of 4,5-dihydro-5-R^F-izoxazol-5-ols takes place under drastic conditions only.

Experimental Part

1. *General.* The 2-(polyfluoroacyl)cycloalkanones **1a**,**f** [13], **1b** [24], **1c** [21][25], **1d** [26], **1e**,**g** [27], and **1h** [25] were synthesized by a *Claisen*-type condensation of cyclopentanone or cyclohexanone and alkyl polyfluoroalkanoates. The 4-ene-1,3-diones **3** were prepared from the corresponding compounds **1** according to the procedure elaborated earlier by us [12]. B.p. and m.p.: not corrected. IR Spectra: *Specord 75-IR* spectrophotometer. NMR Spectra: *Tesla BS-587A* spectrometer (80.02 (^{1}H) and 75.39 MHz (^{19}F)) and *Bruker DPX-200* spectrometer (200.13 (^{1}H), 50.32 (^{13}C), 188.31 MHz (^{19}F); δ in ppm, J in Hz, Me_4Si (^{1}H and ^{13}C) and CCl_3F (^{19}F) as internal standards. *ABMNX* spin system of **2a** calculated from ^{19}F- and ^{1}H-NMR with the program LAOCN-3 [28]. MS: EI, at 70 eV; for **7b**, FAB, glycerine/DMSO, Xe, 8keV; *MAT-8200* spectrometer. Column chromatography (CC): gel (normal phase, *Matrex, Grace GmbH*).

2. *Compounds* **2**, **4**, *and* **5**. 2.1. *General Procedure.* To a soln. of 1,3-diketone (10 mmol) and hydroxylamine (10 mmol; generated *in situ* by treatment of hydrochloride salt (0.7 g, 10 mmol) with Et_3N (1.0 g, 10 mmol)) in propan-2-ol (15 ml), $BF_3 \cdot OEt_2$ (3 drops) was added. The mixture was refluxed (*Table 11*), then cooled, and diluted with H_2O (100 ml).

2.2. *Workup Procedures.* 2.2.1. **2a**,**c**,**e**: The mixture was extracted with $CHCl_3$ (3×10 ml), the combined org. phase dried ($MgSO_4$) and evaporated, the residue crystallized by trituration with cold pentane. Recrystallization (*Table 11*) gave the product as colorless crystals.

2.2.2. **2b**. The mixture was extracted with $CHCl_3$ (3×10 ml), the combined org. phase dried ($MgSO_4$) and evaporated, and the residue crystallized in 24 h. Recrystallization (*Table 11*) gave the product as colorless crystals.

2.2.3. **2d**,**f** *and* **4**. The solid precipitate was filtered, dried, and recrystallized (*Table 11*): **2d**,**f** and **4a**,**b** as colorless crystals and **4c** as yellowish crystals.

2.2.4. **2g**. The mixture was extracted with CH_2Cl_2 (3×10 ml), the combined org. phase dried ($MgSO_4$) and evaporated, and the residue purified by CC (AcOEt). After evaporation of the eluate, the residue was recrystallized (*Table 11*): **2g** as colorless crystals.

2.3. *Reaction of 2-(trifluoroacetyl)cyclopentanone* (**1h**) *with Hydroxylamine.* To a soln. of **1h** (2.0 g, 11 mmol) and hydroxylamine (11 mmol; generated *in situ* by treatment of the hydrochloride salt (0.77 g, 11 mmol) with Et_3N (1.12 g, 11 mmol)) in propan-2-ol (15 ml) was added $BF_3 \cdot OEt_2$ (3 drops). The mixture was refluxed for 7 h. The cooled mixture was poured in H_2O (100 ml), extracted with $CHCl_3$ (3×10 ml), the combined org. phase dried ($MgSO_4$) and evaporated, and the residue purified by CC ($CHCl_3$). The yellow oil obtained after evaporation of the single fraction was a mixture of several CF_3-containing compounds according to the ^{19}F-NMR data. MS: 195 (60, M^+); 178 (30, $[M - OH]^+$), 108 (100, $[M - H_2O - CF_3]^+$), and other fragments, where $M^+ = C_7H_8F_3NO_2^+$.

2.4. *Reaction of (2*E*)-2-Benzylidene-5-(trifluoroacetyl)cyclopentanone* (**3d**) *with Hydroxylamine.* To a soln. of **3d** (0.5 g, 1.9 mmol) and hydroxylamine (1.9 mmol; generated *in situ* by treatment of the hydrochloride salt (0.13 g, 1.9 mmol) with Et_3N (0.19 g, 1.9 mmol)) in propan-2-ol (15 ml), $BF_3 \cdot OEt_2$ (3 drops) was added. The mixture was refluxed for 6 h. The cooled mixture was poured in H_2O (100 ml) and the solid precipitate filtered, dried, and recrystallized from acetone: **5** (0.08 g, 32%) as yellow needles. M.p. 194° ([15]: 192.4°). ^{1}H-NMR ((D_6)DMSO): 3.1 (br. *s*, 2 CH_2); 7.35–7.55 (*m*, 8 H, 2 Ph, 2 =CH); 7.60–7.75 (*m*, 4 H, 2 Ph). MS: 260 (65, M^+), 259 (100, $[M - H]^+$), and other fragments.

Table 11. *Melting and Boiling Points, Reaction Times, Yields, and Elemental Analysis* (HR-MS) *Data of Compounds* **2a**–**g**, **4a**–**c**, **6a**,**b**, *and* **7a**–**c**

	Name	M.p. [°] (solvent)	Formula	[%][a]) or HR-MS [*m*/*z*]				Yield [%]	Reaction time [h]
				C	H	F	N		
2a	3a,4,5,6-Tetrahydro-3-(1,1,2,2-tetrafluoroethyl)-3*H*-cyclopenta[*c*]isoxazol-3-ol	93–95[b])	$C_8H_9F_4NO_2$	*42.55* 42.30	*4.02* 3.99	*33.26* 33.45	*6.19* 6.17	66	2
b	3a,4,5,6-Tetrahydro-3-(nonafluorobutyl)-3*H*-cyclopenta[*c*]isoxazol-3-ol	79–81[b])	$C_{10}H_8F_9NO_2$	HR-MS: 345.0416 (calc. 345.0411); −1.3 ppm (10.0), −0.5 mmu (5.0)				66	15
c	3,3a,4,5,6,7-Hexahydro-3-(trifluoromethyl)-1,2-benzisoxazol-3-ol	98–99[c]) (hexane/toluene 4:1)	$C_8H_{10}F_3NO_2$	*45.92* 45.94	*4.85* 4.82	*27.18* 27.25	*6.82* 6.70	48	10
d	3,3a,4,5,6,7-Hexahydro-3-(1,1,2,2-tetrafluoroethyl)-1,2-benzisoxazol-3-ol	147–148 (hexane/$CHCl_3$ 1:1)	$C_9H_{11}F_4NO_2$	*44.72* 44.82	*4.94* 4.60	*31.86* 31.51	*5.87* 5.81	89	3
e	3-(Heptafluoropropyl)-3,3a,4,5,6,7-hexahydro-1,2-benzisoxazol-3-ol	107.0–107.5[b])	$C_{10}H_{10}F_7NO_2$	*38.89* 38.85	*3.27* 3.26	*43.08* 43.01	*4.48* 4.53	55	2
f	3,3a,4,5,6,7-Hexahydro-3-(1,1,2,2,3,3,4,4-octafluorobutyl)-1,2-benzisoxazol-3-ol	106–107 (hexane/$CHCl_3$ 10:1)	$C_{11}H_{11}F_8NO_2$	*38.77* 38.72	*3.01* 3.25	*44.41* 44.54	*3.95* 4.11	88	10
g	3,3a,4,5,6,7-Hexahydro-3-(tridecafluorohexyl)-1,2-benzisoxazol-3-ol	136–137[b])	$C_{13}H_{10}F_{13}NO_2$	*33.80* 34.00	*2.28* 2.20	*53.90* 53.78	*2.82* 3.05	64	6
4a	(7*E*)-7-Benzylidene-3-(trifluoromethyl)-3,3a,4,5,6,7-hexahydro-1,2-benzisoxazol-3-ol	208–209 (hexane/$CHCl_3$ 3:2)	$C_{15}H_{13}F_3NO_2$	HR-MS: 296.0901 (calc. 296.0898) −0.9 ppm (10.0), −0.3 mmu (5.0)				58	16
b	(7*E*)-3,3a,4,5,6,7-Hexahydro-7-(4-methoxybenzylidene)-3-(trifluoromethyl)-1,2-isoxazol-3-ol	192–193 ($CHCl_3$)	$C_{16}H_{15}F_3NO_3$	HR-MS: 326.1005 (calc. 326.1004); −0.2 ppm (10.0), −0.1 mmu (5.0)				71	16
c	(7*E*)-7-[4-(Dimethylamino)benzylidene]-3,3a,4,5,6,7-hexahydro-3-(nonafluorobutyl)-1,2-benzisoxazol-3-ol	182–186 ($CHCl_3$)	$C_{20}H_{19}F_9N_2O_2$	HR-MS: 490.1322 (calc. 490.1303); −3.9 ppm (10.0), −1.9 mmu (5.0)				15	16
6a	4,5,6,7-Tetrahydro-3-(1,1,2,2,3,3,4,4-octafluorobutyl)-1,2-benzisoxazole	84–85[d])	$C_{11}H_9F_8NO$	*40.65* 40.88	*2.78* 2.81	*47.49* 47.03	*4.22* 4.33	67	5
b	4,5,6,7-Tetrahydro-3-(tridecafluorohexyl)-1,2-benzisoxazole	80–82[e])	$C_{13}H_8F_{13}NO$	HR-MS: 441.0400 (calc. 441.0398); −0.4 ppm (10.0), −0.2 mmu (5.0)				55	5
7a	(7*E*)-7-Benzylidene-4,5,6,7-tetrahydro-3-(trifluoromethyl)-1,2-isoxazole	105–106[b])	$C_{15}H_{12}F_3NO$	HR-MS: 279.0860 (calc. 279.0871); 4.0 ppm (10.0), 1.1 mmu (5.0)				36	4
b	(7*E*)-4,5,6,7-Tetrahydro-7-(4-methoxy-3-sulfobenzylidene)-3-(trifluoromethyl)-1,2-benzisoxazol-1-ium inner salt	>260 (EtOH)	$C_{16}H_{14}F_3NO_5S \cdot 5.5\,H_2O$	*39.81* 39.34	*4.05* *5.12*	–	*2.78* 2.87	31	4
c	(7*E*)-4,5,6,7-Tetrahydro-7-(4-methoxybenzylidene)-3-(trifluoromethyl)-1,2-benzisoxazole	82–84[b])	$C_{16}H_{14}F_3NO_2$	HR-MS: 309.0979 (calc. 309.0977); −0.8 ppm, (10.0), −0.2 mmu (5.0)				54	3

[a]) Found values in italics above calc. values. [b]) Perfluoro-1,1-dimethylcyclohexane (= decafluoro-1,1-bis(trifluoromethyl)cyclohexane). [c]) [5]: 104–106°. [d]) B.p. at 0.5 Torr. [e]) B.p. at 1.0 Torr.

3. *Compounds* **6a**,**b**; 3.1. *General Procedure.* A stirred soln. of **2f**,**g** (3.5 mmol) in conc. H_2SO_4 (5 ml) was heated at 40° (*Table 11*). The mixture was quenched with H_2O (70 ml) and extracted with $CHCl_3$ (3 × 10 ml), the combined org. phase dried ($MgSO_4$) and evaporated to 1/4 of the volume, the residue filtered through a pad of silica gel ($CHCl_3$) the eluate evaporated, and the residue distilled (*Table 11*): colorless liquids.

4. *Compounds* **7a**–**c**. 4.1. **7a**. A stirred soln. of **4a** (0.3 g, 1 mmol) in conc. H_2SO_4 (2 ml) was heated at 75° (*Table 11*). The mixture was quenched with H_2O (50 ml) and extracted with $CHCl_3$ (3 × 10 ml), the combined org. phase dried ($MgSO_4$) and evaporated to 1/4 of the volume, the residue filtered through a pad of silica gel (CH_2Cl_2), the eluate evaporated, and the residue recrystallized (*Table 11*): colorless crystals.

4.2. **7b**. A stirred soln. of **4b** (0.35 g, 1 mmol) in conc. H_2SO_4 (3 ml) was heated at 75° (*Table 11*). The mixture was quenched with H_2O (50 ml) and the solid that had precipitated in 24 h was filtered, dried, and recrystallized twice (*Table 11*): colorless crystals.

4.3. **7c**. To a soln. of **4b** (0.5 g, 1.5 mmol) in AcOH (5 ml), conc. H_2SO_4 (4 drops) was added. The mixture was heated under reflux (*Table 11*), then cooled, poured in H_2O (50 ml), and extracted with $CHCl_3$ (3 × 10 ml).

The combined org. phase was dried ($MgSO_4$) and evaporated to 1/4 of the volume, the residue filtered through a pad of silica gel ($CHCl_3$), the eluate evaporated, and the residue recrystallized (*Table 11*): colorless crystals.

5. *Decomposition of* **2a** *by Heating in* H_2SO_4. A soln. of **2a** (1.0 g, 4.4 mmol) in conc. H_2SO_4 (5 ml) was heated at 40° for 5 h under stirring. The mixture was quenched with H_2O (50 ml) and extracted with $CHCl_3$ (3 × 10 ml), the combined org. phase dried ($MgSO_4$) and evaporated, and pentane (5 ml) added to the residue. The precipitate of starting **2a** (0.2 g) was filtered off, the filtrate evaporated, and the residue of the filtrate distilled to afford 1,3-diketone **1a** (0.2 g, 27%).

6. *X-Ray Crystal-Structure Analysis of* **2a**[1]). Single crystal, crystallized from $CHCl_3$/hexane 4:1. Colorless prisms; $C_8H_9F_4NO_2$ (227.16); 0.7 × 0.5 × 0.3 mm³; monoclinic $P2_1/c$ with $a = 884.2(2)$, $b = 626.40(10)$, $c = 1686.6(5)$ pm, $\beta = 102.69(2)°$, $V = 0.9113(4)$ nm³, $D = 1.656$ g·cm^{-3}, $Z = 4$, difference electron density 0.331 and -0.204 e·Å^{-3}. Measurements at 173(2) K with a *Siemens-P4* diffractometer with graphite monochromated MoK_α radiation (λ 71.073 pm) and the low-temperature device *LT2*; index range $-11 \le h \le 11$, $-8 \le k \le 8$, $-21 \le l \le 21$, 2θ range 3.02 to 27.50°, reflections measured 7602, unique reflections 2086 (R(int) = 0.0380). Completeness to $\theta_{max} = 27.50°$: 99.9%, data/restraints/parameter 2086/0/142. The structure was solved by direct methods and refined by full-matrix least-squares at F^2 with the SHELXL-97 program system [29]. All non-H-atoms were refined anisotropically, the OH proton was refined isotropically, the positions of the other H-atoms were calculated as a riding model. The weighting scheme was $w^{-1} = \sigma^2(F_o)^2 + (0.0498P)^2 + 0.32P$ with $P = 1/3(F_o^2 + 2F_c^2)$. Goodness-of-fit at F^2 1.036; final R values ($I > 2\sigma(I)$): $R_1 = 0.0376$, $wR_2 = 0.0968$; R value (all reflections): $R_1 = 0.0480$, $wR_2 = 0.1019$.

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[1]) Crystallographic data (excluding structure factors) for the structure **2a** have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-179682. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (1223) 336033; e-mail: deposit@ccdc.cam.ac.uk).

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